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Cardiovascular morbidity and associated risk factors in Spanish patients with chronic inflammatory rheumatic diseases attending rheumatology clinics: Baseline data of the CARMA Project

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ABSTRACT

Objective: To establish the cardiovascular (CV) morbidity and associated risk factors for CV disease (CVD) in Spanish patients with chronic inflammatory rheumatic diseases (CIRD) and unexposed individuals attending rheumatology clinics.

Methods: Analysis of data from the baseline visit of a 10-year prospective study [CARdiovascular in rheuMAtology (CARMA) project] that includes a cohort of patients with CIRD [rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA)] and another cohort of matched individuals without CIRD attending outpatient rheumatology clinics from 67 hospitals in Spain. Prevalence of CV morbidity, CV risk factors, and systematic coronary risk evaluation (SCORE) assessment were analyzed.

Results: A total of 2234 patients (775 RA, 738 AS, and 721 PsA) and 677 unexposed subjects were included. Patients had low disease activity at the time of recruitment. PsA patients had more commonly classic CV risk factors and metabolic syndrome features than did the remaining individuals. The prevalence of CVD was higher in RA (10.5%) than in AS (7.6%), PsA (7.2%), and unexposed individuals (6.4%). A multivariate analysis adjusted for the presence of classic CV risk factors and disease duration revealed a positive trend for CVD in RA (OR = 1.58; 95% CI: 0.90–2.76; $p = 0.10$) and AS (OR = 1.77; 95% CI: 0.96–3.27; $p = 0.07$). Disease duration in all CIRD groups and functional capacity (HAQ) in RA were associated with an increased risk of CVD (OR = 2.15; 95% CI: 1.29–3.56; $p = 0.003$). Most patients had a moderate CV risk according to the SCORE charts.

Conclusions: Despite recent advances in the management of CIRD, incidence of CVD remains increased in Spanish subjects with CIRD attending outpatient rheumatology clinics.

Introduction

The prevalence of cardiovascular disease (CVD) in chronic inflammatory rheumatic diseases (CIRDs) is higher than in the general population [1]. This results from the compound effect of traditional cardiovascular (CV) risk factors along with chronic inflammation and a genetic component [2,3].

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Rheumatoid arthritis (RA) is the prototype of chronic inflammatory rheumatic disease associated with accelerated atherosclerosis and increased risk of CV death [1,3–7]. Different studies have shown a higher incidence of CV events and CV mortality in RA patients compared to people of the same age and sex [7–9], similarly to what occurs in type 2 diabetes [10,11]. Overall, patients with RA have a 2–3-fold higher risk of myocardial infarction, even in the absence of traditional CV risk factors, as well as a higher rate of CV mortality (up to 50%) [8,9,12,13].

Consistent with data described in RA, patients with spondyloarthropathies also have a higher risk of CVD than the general population [14,15]. CVD and CV mortality are more common in patients with PsA compared to the general population [16–18]. Besides traditional CV risk factors, the presence of severe psoriasis is an important predictor of CVD in these patients [18]. Therefore, although the role of classic CV risk factors cannot be ruled out [16], the disease by itself appears to be a predictor of CV events, since patients with PsA exhibit increased subclinical atherosclerosis regardless of the presence of classic CV risk factors [19,20]. Ankylosing spondylitis (AS) has also been associated with 1.5–2.0-fold higher mortality rate compared to the general population, which is in great part due to CV complications [14,21,22].

Experts in the field have reiterated the need for adequate stratification of CV risk in patients with CIRD. In this regard, a task force from the European League Against Rheumatism (EULAR) has recommended assessing the risk of CV on an annual basis using the National Guidelines for RA patients [23]. In its absence, the Systematic Coronary Risk Evaluation (SCORE) function model is recommended. The SCORE system estimates the 10-year risk of a fatal atherosclerotic event, including heart attack, stroke, or other occlusive arterial disease and sudden cardiac death [24,25]. EULAR's expert panel stated that the same CV risk stratification procedure should also be applicable to AS and PsA. Risk charts used for the general population, however, may underestimate the actual CV risk in patients with rheumatic diseases. Many RA patients classified as having a moderate risk of CV according to SCORE risk charts had severe atherosclerotic disease. This was manifested by the presence of carotid plaques, when non-invasive tools such as carotid ultrasound were used to assess CV risk in these patients [26,27].

Recent studies have emphasized that tight control of the disease leads to a reduction in the rate of CVD in patients with rheumatic diseases. This is especially true in cases of RA where methotrexate and especially anti-TNF-α drugs have been associated with lowering the risk of CV events [28–30]. Thus, one issue of potential relevance may be the need to establish a CV risk profile for patients with CIRD, with periodic follow-up at rheumatology outpatient clinics. Under such a program, such patients would receive active treatment, many of them undergoing biologic therapy, and, due to this, would not have in most cases active disease.

Having taken all these considerations together, we aimed in the present study to establish the CV morbidity and associated risk factors for CVD in Spanish patients included in the basal visits of the CARdiovascular in rheuMAtology (CARMA) project, a multicenter study designed to evaluate CVD in RA, AS, and PsA subjects attending outpatient rheumatology clinics.

Methods

Study design

Descriptive analysis of baseline data obtained at the first visit during the CARMA project. This is a 10-year prospective study of a cohort of patients with CIRD (RA, AS, and PsA) and a cohort of matched subjects without CIRD attending rheumatology clinics from 67 hospitals in Spain. The purpose of this project is to establish the CV risk profile of Spanish patients with CIRD.

Patient recruitment

Patients with CIRD and individuals with non-inflammatory rheumatic diseases attending outpatient rheumatology clinics from the participating hospitals were invited to take part in the study. The period of recruitment was July 2010 to January 2012.

A probabilistic cluster sampling that ensured that the different rheumatology units in Spain had equal probabilities of being chosen was carried out. We randomly selected 67 Spanish centers with rheumatology units from the database of the Spanish Society of Rheumatology (SER). Recruitment was done by the inclusion of consecutive patients with any of the three aforementioned conditions, regardless of disease severity or duration. The recruited patients fulfilled one of the following inclusion criteria: the 1987 American College of Rheumatology Classification Criteria for RA [31], the modified New York Criteria for Definite AS [32], or the Moll and Wright Criteria for PsA [33].

Exposed and unexposed cohorts were matched by age (± 5 years) and sex at a ratio of 1:1. At the end of the recruitment period, 2986 patients who had met the inclusion criteria had been invited to participate. Of them, 75 declined to participate in the study. The statistical power was estimated using the remaining 2911 patients (775 RA, 738 AS, 721 PsA, and 677 unexposed individuals). The percentage of patients with a SCORE $\geq$ 5% was 6% in the unexposed subjects and 12% in the RA cohort. Based on this assumption, the power of the sample numbering 2911 individuals to detect a statistically significant risk difference of 6%, between the cohorts, was 0.98.

Variables and operative definitions

Both the cohorts were evaluated following international protocols, including standardized definitions and validated questionnaires. Continuous online and *in situ* monitoring of data was performed to verify the quality of the information.

The main variables analyzed were the presence of CV events and the CV risk SCORE. CV events included ischemic heart disease, stroke, peripheral arterial disease, and heart failure. To calculate the CV risk according to the SCORE function, we assessed data on sex, age, smoking, systolic blood pressure (mmHg), and total cholesterol (mg/dL). The risk SCORE was calculated for people aged 40 years and older without CV events. Risk estimates were generated in chart form for both high- and low-risk regions in Europe. Spain was included in the low-risk group [24,25].

Secondary variables were as follows: (1) traditional (classic) CV risk factors (hypertension, dyslipidemia, obesity, smoking, and diabetes); (2) parameters of inflammation and disease activity; (3) sociodemographic variables, comorbidities, and laboratory parameters; and (4) potential confounding factors (disease severity, duration of disease, and therapies). Operative definitions of the primary and secondary variables can be found in Table S1 of the Supplementary material. Variables related to inflammatory activity and severity of CIRD can be found in Supplementary Table S2.

Statistical analysis

Numerical variables with normal distribution were expressed as mean and standard deviations. Variables not normally distributed were expressed as median and interquartile ranges (IQR = p25–p75). Absolute and relative frequencies were calculated for qualitative variables. Prevalence, in conjunction with a

95% confidence interval (CI) for traditional CV risk factors and CV events, was also calculated. SCORE function was calculated for each group. Bivariate analysis was conducted to compare socio-demographic characteristics, traditional CV risk factors, and clinical features of each of the CIRD. The dependent variable was the medical history of CV events (presence or absence). Numerical variables were assessed using the Student *t* test or the Mann–Whitney *U* test. Qualitative variables were assessed by a Chi-square test, Yates correction, or Fisher exact test in 2 × 2 tables.

To study the association between CV events and CIRD, logistic regression models were constructed by calculating odds ratios (OR) and adjusting for potentially confounding factors. The same procedure was carried out to identify specific features of RA, AS, and PsA. The selection of independent variables in the multivariate models was based on clinical judgments and those with $p < 0.20$ in the bivariate analysis, using the ENTER method for each of the models, were included.

All analyses were performed using the SPSS 21.0 statistical program. In the bivariate analysis, statistical significance was assumed at $p < 0.05$, whereas in the multivariate models, it was assumed to be $p \leq 0.10$. This study was performed following the principles outlined in the Helsinki Declaration, and the study protocol was approved by the Ethics Committee for Clinical Research of Galicia, Spain.

Results

Demographic characteristics and traditional CV risk factors

A total of 2911 patients were included in the study: 775 patients with RA, 738 with AS, 721 with PsA, and 677 unexposed individuals with the following diseases: osteoarthritis (30%), osteoporosis (15.2%), and other non-inflammatory diseases (54.8%).

The demographic characteristics are summarized in Table 1. The mean age of patients with RA was higher than in those from the other groups. Although patients with AS were younger, the duration of disease was longer than in the other groups. Unexposed individuals had a higher percentage of secondary and university education (65.9%) than the groups with CIRD, which included more patients with only elementary level education ($p < 0.001$).

Overall, patients with PsA had more commonly classic CV risk factors and features of metabolic syndrome than individuals in the other groups. Smoking history was more commonly observed in those with AS (Table 1).

Disease activity and therapy

Table 1 shows the most relevant data related to disease activity and severity in the different groups of the study. In general,

Table 1
Sociodemographic features, traditional cardiovascular risk factors, and clinical characteristics of the population included in the study

Variables	Rheumatoid arthritis ($n = 775$)	Ankylosing spondylitis ($n = 738$)	Psoriatic arthritis ($n = 721$)	Unexposed matched cohort ($n = 677$)	*p*
Sociodemographic features					
Age at inclusion, years, mean (SD)	57.1 (12.3)	48.1 (11.7)	51.8 (12.0)	54.0 (12.4)	< 0.001
Age at the beginning of disease, years, mean (SD)	45.8 (13.4)	29.7 (11.8)	39.5 (13.3)	48.5 (12.4)	< 0.001
Sex, female, *n* (%)	581 (75.0)	200 (27.1)	327 (45.4)	437 (64.5)	< 0.001
Educational level, *n* (%)					
Elementary	467 (60.9)	318 (43.3)	331 (46.3)	229 (34.1)	
Secondary/university	300 (39.1)	416 (56.7)	383 (53.7)	443 (65.9)	< 0.001
Traditional CV risk factors					
BMI, kg/m^2, mean (SD)	26.9 (4.8)	27.4 (4.4)	28.2 (4.7)	26.7 (4.4)	< 0.001
Abdominal perimeter, mean (SD)	93.7 (7.0)	96.3 (12.9)	97.6 (13.0)	93.5 (12.9)	< 0.001
Hypertension, *n* (%)	236 (30.5)	190 (25.7)	213 (29.5)	158 (23.3)	0.008
Hypercholesterolemia, *n* (%)	238 (30.7)	199 (27)	257 (35.6)	224 (33.1)	0.003
Diabetes, *n* (%)	60 (7.8)	56 (7.6)	66 (9.2)	34 (5.0)	0.030
Obesity (BMI ≥ 30), *n* (%)	180 (23.2)	186 (25.2)	209 (29.1)	147 (21.8)	0.010
Smoking status, *n* (%)					
Current smokers	189 (24.4)	254 (34.4)	157 (21.8)	143 (21.2)	
Past smokers	202 (26.1)	240 (32.5)	227 (31.5)	176 (26.0)	< 0.001
Never smokers	384 (49.5)	244 (33.1)	337 (46.7)	357 (52.8)	
Clinical characteristics					
Disease duration, years	8.0 (3.0–14.0)	15.0 (8.0–26.0)	9.0 (4.0–16.0)	2.0 (0.0–6.0)	< 0.001
DAS28-ESR	3.1 (2.3–4.0)	–	2.9 (2.0–3.8)	–	0.002
BASDAI (0–10)	–	3.5 (1.7–5.3)	–	–	–
HAQ (1–3)	0.5 (0.1–1.1)	–	0.4 (0.0–0.9)	–	< 0.001
BASFI (0–10)	–	3.1 (1.3–5.2)	–	–	–
ESR, mm/first hour	17.0 (9.0–29.0)	10.0 (6.0–21.0)	12.0 (6.0–21.0)	10.0 (5.0–18)	< 0.001
CRP, mg/L	3.1 (1.2–8.0)	3.6 (1.6–8.9)	2.9 (1.4–6.1)	1.9 (1.3–3.3)	< 0.001
RF positive, *n* (%)	528 (68.1)	–	–	–	–
ACPA positive, *n* (%)	482 (62.2)	–	–	–	–
HLA-B27, *n* (%)	–	561 (76)	–	–	–
Erosions (RA), *n* (%)	352 (45.4)				–
Biologic DMARD, *n* (%)	313 (40.4)	349 (47.4)	300 (41.7)	–	< 0.001
Synthetic DMARD, *n* (%)	674 (87.0)	239 (32.4)	536 (74.5)	–	< 0.001
NSAID, *n* (%)	309 (39.9)	431 (58.5)	329 (45.9)	142 (21.0)	< 0.001
GC, *n* (% ever treated)	357 (46.1)	59 (8.0)	129 (17.9)	–	< 0.001

Data expressed as median (IQR) unless specified. Categorical variables are expressed as number (*n*) and percentage (%). SD: standard deviation; ACPA: anti-cyclic citrullinated peptide antibodies; BASDAI (0–10): Bath Ankylosing Spondylitis (AS) Disease Activity Score; BASFI (0–10): Bath AS Functional Index; BMI: body mass index; CRP: C-reactive protein; CV: cardiovascular; DAS28-ESR: Disease Activity Score using 28 joints-erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs; GC: glucocorticoids; HAQ (0–3): Health Assessment Questionnaire; HLA-B27: histocompatibility antigen HLA-B27; NSAID: non-steroidal anti-inflammatory drugs; RA: rheumatoid arthritis; RF: rheumatoid factor.

patients included in the project had low disease activity at the time of recruitment. In keeping with these findings, acute-phase reactant [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] values and functionality scores [Health Assessment Questionnaire (HAQ) and Bath Ankylosing Spondylitis Functional Index (BASFI)] showed low values. In this regard, almost half of the patients with CIRD were undergoing biologic therapies at that time. Nonetheless, almost half of the patients with RA had received or were taking low-dose prednisone.

Prevalence of CV events

Figure 1 shows the prevalence of CVD in the different cohorts. The overall prevalence of CVD in RA was 10.5% (20.1% in men and 7.2% in women). A lower prevalence was found in the three other groups (AS, 7.6%; PsA, 7.2%; and unexposed individuals, 6.4%). In most cases, CV events occurred after diagnosis of CIRD (Fig. 1).

Clinical risk factors associated with CVD

Bivariate analysis showed direct correlations between the age at symptom onset, disease duration, educational level, smoking habit (greater risk in ex-smokers), and the development of CV events (Table 2). This was also the case with traditional CV risk factors such as diabetes, hypertension, and hypercholesterolemia in both CIRD patients and unexposed individuals (Fig. 2). Interestingly, HAQ was associated with the occurrence of CV events in both RA and PsA patients. Furthermore, an association between CV events and structural damage, manifested by the presence of erosions in RA and coxitis in patients with AS, was also found (Table 2).

Multivariate analysis showed a direct correlation between RA and risk of CVD (adjusted OR = 1.58; 95% CI: 0.90–2.76; $p = 0.10$). Similar results were observed in patients with AS (adjusted OR = 1.77; 95% CI: 0.96–3.27; $p = 0.07$). Additional associations with CVD were the age at recruitment, male gender, past history of smoking in AS, disease duration, and some traditional CV risk factors (Table 3). Hypertension and hypercholesterolemia were significantly associated with CVD in all groups. However, diabetes was found to be significantly associated only with RA (adjusted OR = 2.56; 95% CI: 1.06–6.18; $p = 0.04$).

Multivariate analysis for each of the CIRD groups confirmed associations with disease duration and most CV risk factors. Nevertheless, association with HAQ was only observed in RA patients (adjusted OR = 2.15; 95% CI: 1.29–3.56; $p < 0.01$) (Table 3).

SCORE results

To calculate the CV risk according to SCORE charts, only patients aged 40 years and older without a previous history of CV events at the time of assessment were included in the analysis. Thus, 52 patients with such a history of CV events were excluded.

The frequency of a high or very high CV risk ($\geq 5\%$) was greater in the RA cohort (21%) compared to other groups (14.4% in PsA patients and unexposed individuals and 12% in AS patients).

Nevertheless, most CIRD patients and unexposed individuals were included within the category of moderate CV risk as the SCORE ranged between $\geq 1\%$ and $< 5\%$ (Table 4). The highest

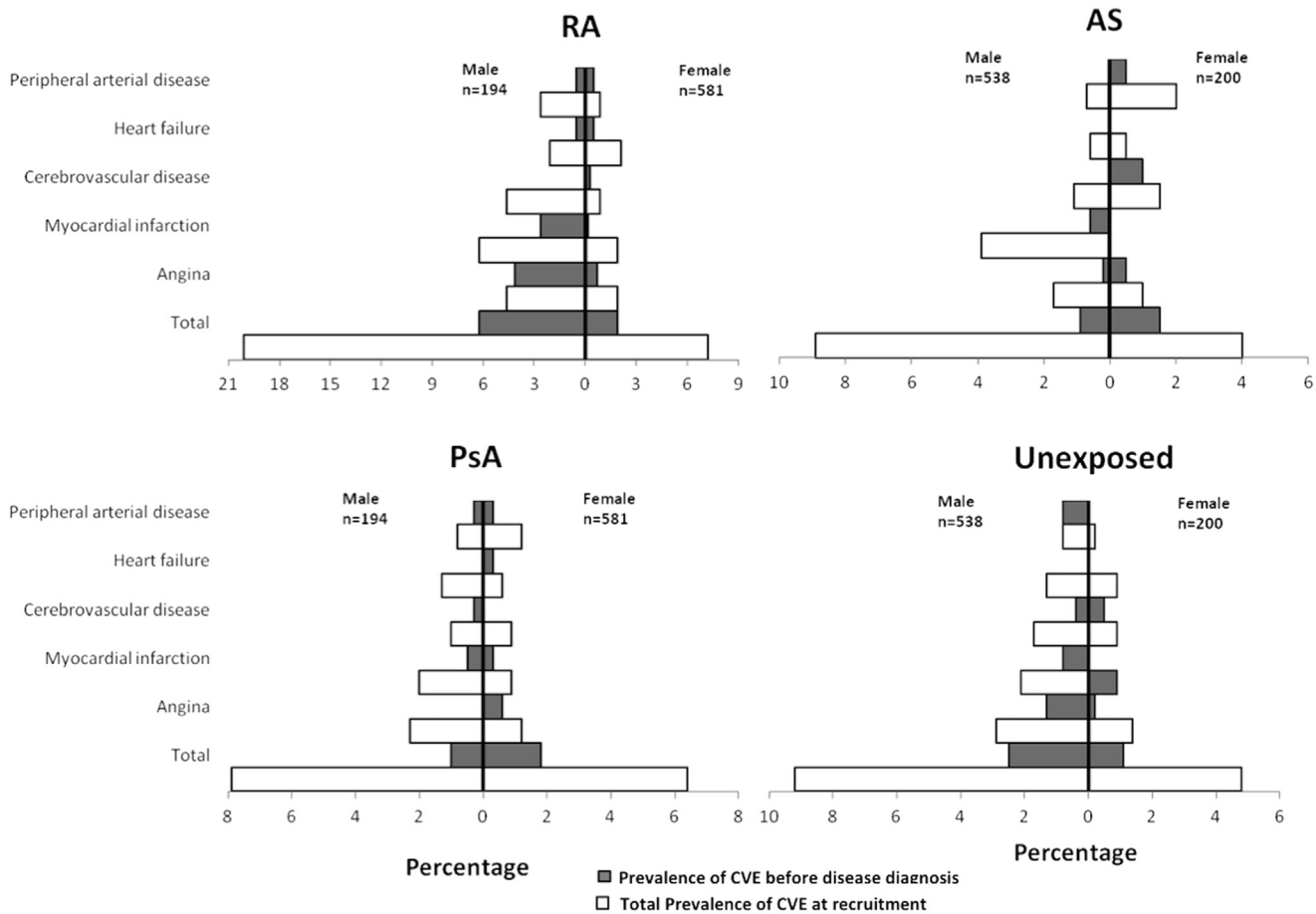

Fig. 1. Prevalence of cardiovascular events in both exposed (RA, AS, and PsA) and unexposed cohorts. Gray boxes represent prevalence of cardiovascular events before disease diagnosis (for each disease). Empty boxes represent total prevalence at the time of recruitment.

Table 2
Bivariate analysis according to each specific entity and the occurrence of cardiovascular events

Variables	All patients			Rheumatoid arthritis			Ankylosing spondylitis			Psoriatic arthritis			Unexposed matched cohort		
	Total	CVE	No CVE	CVE	No CVE	*p*	CVE	No CVE	*p*	CVE	No CVE	*p*	ECV	No ECV	*p*
Female, *n* (%)	1520 (53.2)	51 (37.5)	1469 (53.9)	25 (58.1)	545 (76.9)	0.009	4 (10.5)	193 (27.9)	0.031	9 (30.0)	312 (45.8)	0.129	13 (52.0)	419 (65.4)	0.246
Age at onset of symptoms, years, mean (SD)	40.5 (14.5)	45.8 (16.9)	40.3 (14.3)	49.1 (13.3)	45.1 (13.1)	0.053	34.9 (13.9)	29.3 (11.5)	0.019	45.6 (17.7)	39.0 (12.9)	0.051	56.8 (17.1)	48.1 (12.0)	0.001
Educational level, *n* (%)															
Elementary	1652 (58.3)	102 (75.0)	1550 (57.4)	35 (81.4)	473 (67.5)	0.083	22 (57.9)	392 (57.0)	1.000	25 (83.3)	394 (58.4)	0.011	20 (80.0)	291 (45.8)	0.002
Secondary/ university	1184 (41.7)	34 (25.0)	1150 (42.6)	8 (18.6)	228 (32.5)		16 (42.1)	296 (43.0)		5 (16.7)	281 (41.6)		5 (20.0)	345 (54.2)	
Smoking, *n* (%)															
Never	1300 (45.5)	55 (40.4)	1245 (45.7)	23 (53.5)	349 (49.2)	0.002	4 (10.5)	236 (34.1)	< 0.001	13 (43.3)	321 (47.1)	0.097	15 (60.0)	339 (53.0)	0.516
Past smokers	823 (28.8)	64 (47.1)	759 (27.9)	18 (41.9)	177 (25.0)		25 (65.8)	213 (30.8)		14 (46.7)	206 (30.2)		7 (28.0)	163 (25.5)	
Current smokers	735 (25.7)	17 (12.5)	718 (26.4)	2 (4.7)	183 (25.8)		9 (23.7)	243 (35.1)		3 (10.0)	154 (22.6)		3 (12.0)	138 (21.6)	
Family history of IHD, *n* (%)	349 (12.4)	21 (15.6)	328 (12.2)	8 (18.6)	83 (11.8)	0.274	5 (13.2)	94 (13.7)	1.000	5 (16.7)	72 (10.7)	0.362	3 (12.5)	79 (12.7)	1.000
Obesity, *n* (%)	702 (24.6)	51 (37.5)	651 (24.0)	10 (23.3)	160 (22.6)	1.000	17 (44.7)	166 (24.0)	0.007	14 (46.7)	189 (27.8)	0.043	10 (40.0)	136 (21.3)	0.049
Diabetes, *n* (%)	198 (6.9)	30 (22.1)	168 (6.2)	10 (23.3)	44 (6.2)	< 0.001	8 (21.1)	44 (6.4)	0.004	9 (30.0)	53 (7.8)	0.001	3 (12.0)	27 (4.2)	0.097
Hypertension, *n* (%)	755 (26.4)	97 (71.3)	658 (24.2)	28 (65.1)	190 (26.8)	< 0.001	24 (63.2)	160 (23.1)	< 0.001	24 (80.0)	179 (26.3)	< 0.001	21 (84.0)	129 (20.1)	< 0.001
Hypercholesterol, *n* (%)	886 (31.0)	99 (72.8)	787 (28.9)	23 (53.5)	203 (28.6)	0.001	31 (81.6)	162 (23.4)	< 0.001	26 (86.7)	223 (32.7)	< 0.001	19 (76.0)	199 (31.0)	< 0.001
Disease duration, years	8.0 (3.0–16.0)	15.5 (7.0–27.7)	8.0 (3.0–15.0)	13.0 (8.0–21.0)	8.0 (3.0–14)	< 0.001	23 (13.0–32.5)	15.0 (8.0–26)	0.002	19 (6.7–28.2)	9.0 (4.0–16.0)	0.002	5.0 (0.5–17.0)	2.0 (0.0–6.0)	0.017
ESR, mm/first hour	12.0 (6.0–22)	12.0 (6.7–24)	12.0 (6.0–22.0)	18.0 (7.7–28.2)	17.0 (9.0–30.0)	0.563	10.5 (6.7–19.2)	10.0 (6.0–21)	0.694	10.0 (7–30.2)	12.0 (6.0–20.5)	0.491	9.0 (4.2–23.7)	10.0 (5.0–18.0)	0.722
CRP, mg/L	2.9 (1.1–6.6)	4.0 (1.3–8.0)	2.9 (1.1–6.4)	2.3 (1.0–6.1)	3.1 (1.2–8.0)	0.217	6.0 (2.6–7.8)	3.4 (1.5–8.9)	0.181	3.6 (1.5–8.5)	2.9 (1.3–6.0)	0.334	2.0 (1.1–14.5)	1.9 (1.0–3.2)	0.040
NSAID, *n* (%)	1198 (41.9)	54 (39.7)	1144 (42.0)	17 (39.5)	283 (39.9)	1.000	22 (57.9)	407 (58.8)	1.000	10 (33.3)	319 (46.8)	0.206	5 (20.0)	135 (21.1)	1.000
Glucocorticoids, *n* (%)	526 (24.0)	31 (27.7)	495 (23.8)	23 (53.5)	319 (45.0)	0.353	2 (5.3)	56 (8.1)	0.760	6 (20.0)	120 (17.6)	0.929	–	–	–
DMARD, *n* (%)	1418 (49.6)	76 (55.9)	1342 (49.3)	38 (88.4)	615 (86.7)	0.940	14 (36.8)	223 (32.2)	0.679	24 (80.0)	504 (74.0)	0.602	–	–	–
Biologics, *n* (%)	951 (33.3)	43 (31.6)	908 (33.3)	21 (48.8)	285 (40.2)	0.337	13 (34.2)	333 (48.1)	0.132	9 (30.0)	290 (42.6)	0.239	–	–	–
RF+, *n* (%)	–	–	–	33 (76.7)	542 (76.4)	1.000	–	–	–	–	–	–	–	–	–
ACPA+, *n* (%)	–	–	–	25 (58.1)	421 (59.4)	0.999	–	–	–	–	–	–	–	–	–
Erosions, *n* (%)	–	–	–	28 (65.1)	312 (44.0)	0.011	–	–	–				–	–	–
DAS28-ESR	3.0 (2.2–3.9)	3.1 (2.3–4.1)	3.0 (2.1–3.9)	3.2 (2.4–4.2)	3.0 (2.3–4.0)	0.260	–	–	–	2.9 (2.1–3.5)	2.9 (2.0–3.8)	0.806	–	–	–
HAQ (1–3)	0.5 (0.0–1.1)	0.7 (0.3–1.6)	0.5 (0.0–1.1)	1.1 (0.5–1.6)	0.5 (0.1–1.1)	< 0.001	–	–	–	0.7 (0.1–1.2)	0.4 (0.0–0.9)	0.028	–	–	–
HLA-B27, *n* (%)	–	–	–	–	–	–	28 (73.7)	527 (76.2)	0.879	–	–		–	–	–
Coxitis, *n* (%)	–	–	–	–	–	–	29 (76.3)	385 (55.6)	0.019	–	–		–	–	–
BASDAI (1–10)	–	–	–	–	–	–	2.8 (1.5–4.7)	3.5 (1.8–5.3)	0.411	–	–	–	–	–	–
BASFI (1–10)	–	–	–	–	–	–	3.4 (1.1–6.2)	3.0 (1.3–5.1)	0.793	–	–	–	–	–	–
Enthesopathy, *n* (%)	417 (29.4)	19 (28.4)	398 (29.4)	–	–	–	15 (39.5)	225 (32.8)	0.500	4 (13.3)	173 (25.9)	0.210	–	–	–

Data expressed as median and interquartile range (IQR) unless specified. Categorical variables are expressed as number (*n*) and percentage (%). SD: standard deviation; ACPA: anti-cyclic citrullinated peptide antibodies; BASDAI (0–10): Bath Ankylosing Spondylitis (AS) Disease Activity Score; BASFI (0–10): Bath AS Functional Index; BMI: body mass index; CRP: C-reactive protein; CVE: cardiovascular events; DAS28-ESR: Disease Activity Score using 28 joints-erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs; HAQ (0–3): Health Assessment Questionnaire; HLA-B27: histocompatibility antigen HLA-B27; IHD: ischemic heart disease; NSAID: non-steroidal anti-inflammatory drugs; RA: rheumatoid arthritis; RF: rheumatoid factor.

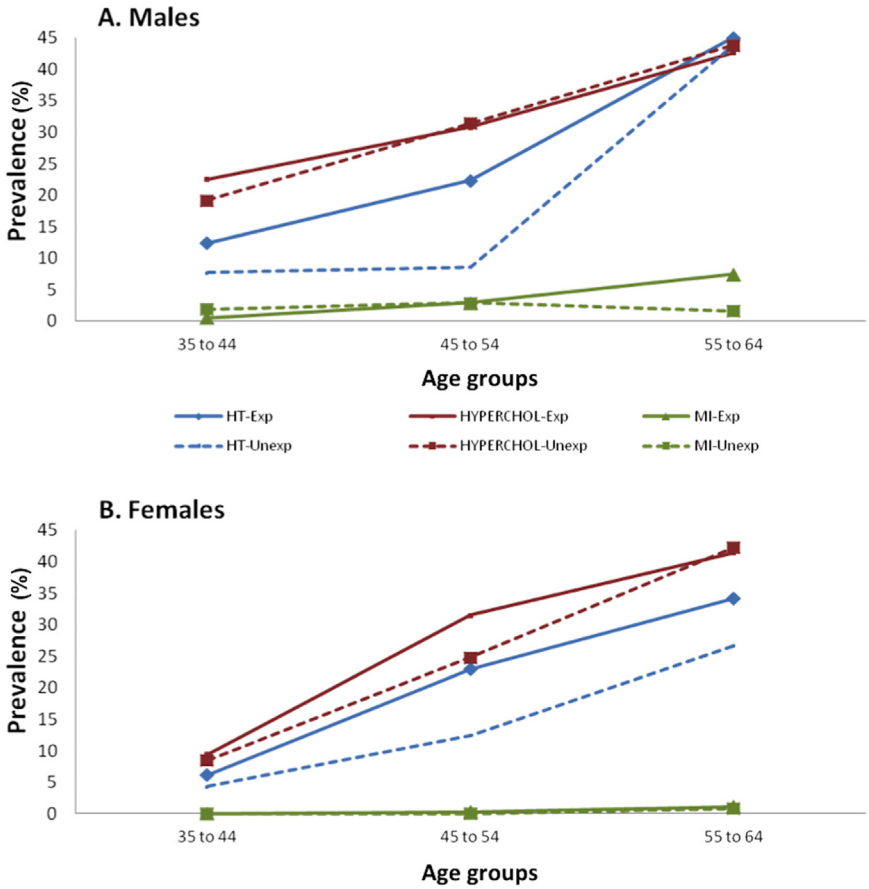

Fig. 2. Prevalence of hypertension, hypercholesterolemia, and acute myocardial infarction in the CIRD cohort (Exp) and in the unexposed matched cohort (Unexp). (Upper panel) males and (Lower panel) females. HT: hypertension; HYPERCHOL: hypercholesterolemia; MI: myocardial infarction.

mean basal SCORE results were found in men with RA, followed by those with PsA and unexposed subjects. Additional information is shown in Table 4.

Discussion

Baseline results from the CARMA project indicate that the risk of CVD in Spanish patients with CIRD attending outpatient rheumatology clinics is higher than in non-inflammatory disease patients. This seems to be particularly true for RA and AS patients. In this regard, although in the adjusted models the risk for CV events in RA and AS groups reached levels that may be considered marginally significant, we feel that they are of considerable value. Patients from the study were periodically followed by rheumatologists at medical centers and at the time of recruitment had generally mild disease activity. Most of them had low levels of disability, and the acute-phase reactants were within the normal range. Taking all these considerations together, we believe that these factors may potentially exert some influence in decreasing the actual prevalence of CVD in Spanish CIRD patients.

In line with the above, it is interesting to note the high number of patients undergoing biologic therapy, which exceeded 40% in the three inflammatory conditions included in the CIRD cohort. This fact may explain the reasonable degree of control over the disease achieved in our patients. This may have lead, in turn, to a reduction in the inflammatory burden and, consequently, to a decrease in the prevalence of CV events. Interestingly, results from the British Society for Rheumatology Biologics Register (BSRBR) have revealed that the risk of myocardial infarction is lower in patients RA who respond to anti-TNF-α therapy compared to non-responders [29]. Since chronic inflammation plays a pivotal role in the increased risk of subclinical atherosclerosis and CV morbidity and mortality in RA [3,4,34], lessening the CV risk associated with anti-TNF-α therapy in other studies highlights the potential cardioprotective effect of these biologic agents when mediated by reductions in the inflammatory burden [30].

As previously reported [2,16], classic CV risk factors were associated with CVD in this Spanish cohort of CIRD patients. Furthermore, disease duration was also associated with an increased risk of CVD in those patients included in the CARMA project. This is keeping with various studies that have supported the relevance of disease duration in the risk of CVD in RA patients [6,35].

As observed in the general population, the prevalence of CVD in patients with CIRD included in the Spanish study was higher in men. In our study, we did not observe a significant association between the educational levels and CVD in these patients.

Since in the general population both active and past smokers have a higher prevalence of myocardial infarction than non-smokers, the higher CV risk among past smokers in this cohort of CIRD patients, in particular in the group of AS, may be in part the result of a reversal causality, specifically a previous history of CV events, which is one of the main reasons for quitting smoking.

A point of special interest in chronic inflammatory diseases is the paradoxical association between lipids and CVD risk. Although in the general population the risk to develop atherosclerosis increases progressively with increasing low-density lipoprotein (LDL) cholesterol levels and declines with increasing levels of high-density lipoprotein (HDL) cholesterol, the presence of a proinflammatory state leads to a decrease of total, HDL, and LDL

Table 3
Multivariate analysis of cardiovascular disease in the cohort of patients with chronic inflammatory rheumatic diseases

Variables	All patients (n = 2234)			Rheumatoid arthritis (n = 775)			Ankylosing spondylitis (n = 738)			Psoriatic arthritis (n = 721)		
	OR[c] (95% CI)	OR[adj] (95% CI)	p	OR[c] (95% CI)	OR[adj] (95% CI)	p	OR[c] (95% CI)	OR[adj] (95% CI)	p	OR[c] (95% CI)	OR[adj] (95% CI)	p
Disease (ref. unexposed)												
RA	1.56 (0.94–2.58)[a]	1.58 (0.90–2.76)	0.100	–	–	–	–	–	–	–	–	–
AS	1.41 (0.84–2.36)	1.77 (0.96–3.27)	0.068	–	–	–	–	–	–	–	–	–
PsA	1.13 (0.66–1.94)	0.96 (0.53–1.76)	0.905	–	–	–	–	–	–	–	–	–
Age at inclusion	1.09 (1.07–1.11)[b]	1.07 (1.05–1.09)	< 0.001	–	–	–	–	–	–	–	–	–
Age onset of symptoms				1.02 (1–1.05)[a]	1.03 (0.99–1.07)	0.122	1.04 (1.01–1.07)[b]	1.08 (1.03–1.13)	0.001	1.04 (1.01–1.07)[b]	1.09 (1.04–1.15)	0.001
Sex (ref. male)	0.51 (0.36–0.73)[b]	0.46 (0.29–0.73)	0.001	0.42 (0.22–0.79)[b]	0.32 (0.14–0.76)	0.010	0.30 (0.11–0.87)[b]	0.4 (0.12–1.34)	0.137	0.51 (0.23–1.12)[a]	2.25 (0.82–6.15)	0.114
Educational level (ref. elementary)	0.45 (0.30–0.67)[b]	0.77 (0.5–1.20)	0.254	0.47 (0.22–1.04)[a]	0.63 (0.26–1.53)	0.306	0.96 (0.5–1.87)	1.71 (0.78–3.76)	0.180	0.28 (0.11–0.74)[b]	0.58 (0.19–1.84)	0.357
Smoking (ref. never)												
Smokers	0.54 (0.31–0.93)[b]	0.7 (0.37–1.29)	0.251	0.17 (0.04–0.71)[b]	0.26 (0.05–1.25)	0.093	219 (0.66–7.19)	1.64 (0.44–6.08)	0.104	0.48 (0.14–1.71)	1.35 (0.31–5.91)	0.690
Past smokers	1.91 (1.32–2.77)[b]	1.42 (0.9–2.25)	0.132	1.54 (0.81–2.94)	1.68 (0.72–3.92)	0.229	6.93 (2.37–20.22)[b]	3.39 (1.05–10.93)	0.041	1.68 (0.7–3.64)	1.84 (0.67–5.06)	0.236
Family history of IHD (ref. no)	1.33 (0.82–2.14)	1.24 (0.72–2.13)	0.436	1.72 (0.77–3.82)	1.31 (0.53–3.24)	0.563	0.96 (0.36–2.51)	0.84 (0.27–2.66)	0.770	1.67 (0.62–4.49)	2.01 (0.61–6.64)	0.253
Obesity (ref. no)	1.91 (1.33–2.73)[b]	1.24 (0.83–1.85)	0.304	1.04 (0.50–2.16)	0.76 (0.33–1.76)	0.521	2.56 (1.32–4.98)[b]	1.57 (0.71–3.49)	0.266	2.27 (1.09–4.74)[b]	2.07 (0.78–5.45)	0.143
Diabetes (ref. no)	4.30 (2.79–6.65)[b]	1.40 (0.85–2.29)	0.185	4.58 (2.12–9.90)[b]	2.56 (1.06–6.18)	0.036	3.93 (1.70–9.08)[b]	1.15 (0.42–3.12)	0.791	5.08 (2.22–11.64)[b]	1.27 (0.46–3.47)	0.640
Hypertension (ref. no)	7.81 (5.33–11.44)[b]	2.85 (1.86–4.36)	< 0.001	5.1 (2.66–9.76)[b]	2.36 (1.12–4.98)	0.024	5.70 (2.88–11.28)[b]	2.01 (0.89–4.57)	0.095	11.22 (4.51–27.89)[b]	3.23 (1.15–9.05)	0.026
Hypercholesterolemia (ref. no)	6.58 (4.47–9.69)[b]	4.15 (2.73–6.33)	< 0.001	2.87 (1.54–5.33)[b]	2.20 (1.09–4.45)	0.028	14.5 (6.26–33.52)[b]	8.66 (3.54–21.24)	< 0.001	13.35 (4.60–38.72)[b]	6.12 (1.98–19.25)	0.002
Disease duration	–	–	–	1.05 (1.03–1.08)[b]	1.06 (1.01–1.11)	0.025	1.04 (1.01–1.06)[b]	1.06 (1.06–1.01)	0.014	1.08 (1.04–1.11)[b]	1.15 (1.072–1.228)	< 0.001
HAQ	–	–	–	2.18 (1.44–3.28)[b]	2.15 (1.29–3.56)	0.003	–	–	–	2.0 (1.2–3.34)[b]	1.08 (0.54–2.18)	0.821
Erosions (ref. no)	–	–	–	2.38 (1.25–4.53)[b]	1.60 (0.78–3.30)	0.202	–	–	–	–	–	–
Coxitis (ref. no)	–	–	–	–	–	–	2.57 (1.2–5.51)[b]	1.86 (0.79–4.36)	0.155	–	–	–

Adjusted for sex, age at inclusion, age at onset of symptoms, educational level, smoking habit, family history of ischemic heart disease (IHD), disease duration, erosions (in RA and PsA), HAQ, and traditional CV risk factors (obesity, hypertension, diabetes mellitus, and dyslipidemia).
OR: odds ratio; OR[c]: crude OR; OR[adj]: adjusted OR.

[a] Significant variables at 90% confidence interval (CI) ($p \leq 0.10$).
[b] Significant variables at 95% CI ($p < 0.05$) in the crude, non-adjusted analysis.

Table 4
Assessment of the SCORE function in the CARMA study population

	Traditional cardiovascular risk factors[a]					Baseline SCORE index (mean)
	Sex	Smoking	Age, mean (years)	SBP, mean (mmHg)	Cholesterol[b] mean (mg/dL)	
Rheumatoid arthritis ($n = 693$)	Male	No	64.2	140.9	193.9	4.2
		Yes	54.7	135.6	196.2	3.2
	Female	No	60.1	133.9	209.3	1.3
		Yes	53.7	126.4	210.9	0.9
Ankylosing spondylitis ($n = 545$)	Male	No	54.2	133.2	197.1	1.5
		Yes	51.6	133.3	207.9	2.4
	Female	No	54.0	128.5	204.4	0.5
		Yes	50.1	127.1	201.6	0.5
Psoriatic arthritis ($n = 598$)	Male	No	55.7	135.4	200.1	1.8
		Yes	52.9	136.3	200.5	2.8
	Female	No	56.4	134.9	211.2	0.8
		Yes	52.1	125.6	205.2	0.7
Unexposed subjects ($n = 578$)	Male	No	57.1	131.5	203.7	2
		Yes	53.0	130.9	217.7	2.8
	Female	No	58.7	127.1	213.0	0.9
		Yes	54.2	125.1	219.5	1.0

SCORE: Systematic Coronary Risk Evaluation; SBP: systolic blood pressure.

[a] Only patients ≥40 years of age without previous history of cardiovascular events (CVE) at the time of assessment were included in the analysis.

[b] Total cholesterol.

cholesterol levels in RA patients with active disease [36]. However, in the current investigation, hypercholesterolemia was consistently associated with CVD. Intuitively, this contrasting finding/disparity is in a way expected in view of the tight control of patients included in this study with mild disease activity at the time of recruitment.

Interestingly, although in bivariate analysis obesity was associated with CV events in AS, PsA, and unexposed subjects, this was not the case in RA. Further, obesity was not related to CV events in any of the groups once other risk factors were considered in multivariable analysis. In this regard, a recent study has shown that obesity was associated with carotid atherosclerosis in white patients with RA, but this relationship was explained by metabolic risk factors [37].

The frequency of positive rheumatoid factor and anti-CCP antibodies, as well as the presence of radiographic erosions in the cohort of RA patients of the CARMA project, was similar to those reported in other series of Spanish RA patients [38,39]. This was also true of the frequency of HLA-B27 [40]. However, no significant association between these data and the occurrence of CVD was found. In addition, although the presence of coxitis was associated with CVD in the bivariate analysis, this association did not reach significance in the multivariate analysis. In contrast, an association of current HAQ with the presence of CV events in RA was observed both in the bivariate and multivariate analyses. This finding may be of potential relevance since HAQ reflects damage accrual over time, which reflects the persistence of a chronic proinflammatory state leading to increased atherogenic burden. In this regard, some authors have linked HAQ results with mortality and long-term structural damage and work disability [41,42]. Moreover, a relationship between HAQ and comorbidity has been found in RA [43,44]. These studies suggest that high HAQ values may serve as accurate predictors of mortality and risk of CVD.

Regarding Systematic Coronary Risk Evaluation, the mean SCORE was higher in patients with CIRD than in the unexposed cohort. However, most patients were included in the category of moderate CV risk when SCORE risk charts were used. These results are in agreement with recent data from a population-based study showing that approximately 60% of patients with RA fall into the category of moderate CV risk according to SCORE risk charts. Regrettably, more than 50% of them had carotid plaques when carotid ultrasound studies were performed, indicating that tools generally used for the stratification of the CV risk in the general population may underestimate the actual CV risk in patients with CIRD [26,27]. Interestingly, a recent study has demonstrated that RA patients with active disease have higher vulnerability of carotid plaques than those in clinical remission [45]. Therefore, both tight control of the disease and adequate CV risk stratification should be carried out in patients with CIRD to minimize the increased risk of CV death [46,47].

The nature of our study may suffer certain limitations, as we have studied a population periodically assessed at rheumatology units. This fact possibly reduces the risk of CVD in this cohort of CIRD patients. Nevertheless, our results indicate that despite recent advances in the management of chronic inflammatory diseases, CVD remains increased in Spanish patients with CIRD attending rheumatology outpatient clinics. Another potential limitation of our study is that the unexposed cohort used for comparison is not a completely healthy cohort, since it included patients with chronic diseases such as osteoarthritis and osteoporosis, which by themselves may cause some increase in CV mortality. Nevertheless, these considerations, despite whatever limitation they may impose on our study, still underscore the likelihood that there is an increased risk of CVD in patients with CIRD, even if they are adequately controlled.

In summary, we present here the baseline analysis of a 10-year prospective study from a cohort of patients with CIRD attending outpatient rheumatology clinics in Spain, where the prevalence of CVD in RA and AS was higher than that observed in an unexposed cohort.

Conclusion

Our results indicate that, despite recent advances in the management of chronic inflammatory rheumatic diseases, the prevalence of cardiovascular disease (CVD) remains high in Spanish subjects with CIRD who are followed up periodically at outpatient rheumatology clinics. It is of particular relevance as almost half of them were receiving biological therapy and most patients had low disease activity at the time of assessment. Classic CV risk factors and disease duration are associated with an increased risk of CVD. Furthermore, HAQ is independently associated with the occurrence of CV events in patients with RA. Surprisingly, most patients with increased prevalence of CV events had a moderate CV risk according to the SCORE charts.

Authors' contributions

Santos Castañeda and Maria A. Martin-Martinez performed the data analysis and drafted the manuscript. Carlos Gonzalez-Juanatey helped develop the study protocol and the manuscript and also assisted in data interpretation. Javier Llorca helped design the study protocol, interpret the data, strengthen the manuscript, and also performed the statistical analysis. Maria J. Garcia-Yebenes, Sabina Perez-Vicente, and Jesus T. Sanchez-Costa helped interpret the data and improve the manuscript. Federico Diaz-Gonzalez helped interpret the data and strengthen the manuscript. Miguel A. Gonzalez-Gay helped design and developed the CARMA project, assisted in data interpretation, and was responsible for the final draft of the manuscript. All the authors have given their approval to the final version.

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Appendix A. Supplementary Materials

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.semarthrit.2014.12.002.

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